PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Status of cognitive frailty in elderly patients with chronic kidney disease and construction of a risk prediction model: a cross-sectional study
AUTHORS	Luo, Baolin; Luo, zebing; Zhang, Xiaoyun; Xu, Meiwan; Shi, Chujun

VERSION 1 – REVIEW

REVIEWER	Babic, Frantisek Technical University of Košice Faculty of Electrical Engineering and Informatics
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	The paper focuses on an important issue related to elderly care. The authors used data from 2 hospitals for data-based decision model generation using an artificial intelligence approach. The design of the study looks OK, all steps are clearly described. page 5 "Studies show that compared with traditional prediction models, artificial neural networks have stronger predictive ability and can efficiently identify diseases and high-risk groups in various systems" - but this strong statement is supported only by one existing study. It is an open question whether other machine learning methods would not provide interesting results for the experts, mainly from the point of explainability and interpretability. page 10 "and the 425 samples were randomly divided into a training set, validation set, persistence set at a ratio of 5:3:2" - it is not clear if the authors used stratified division, i.e., the ratio for the target variable was the same in all three sets. page 3 "... limitations of this study" - it will be important to consider also the unbalanced ratio of the target variable.

REVIEWER	Singh, Narinder Pal Max Super Speciality Hospital Vaishali
REVIEW RETURNED	06-Feb-2022

GENERAL COMMENTS	There are some errors in the grammar in Data collection - Please use Past Tense instead of Present The study lacks generalizability as most subjects are primary school graduates and majority have low income. These can be confounding There is no control group which can compare the frailty in elderly without CKD.

	Authors have not mentioned how they diagnosed CKD . It is now very well known that AGING per say can cause lowering of eGFR when calculated and may not represent a TRUE CKD(.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4693148/) Authors have also included CKD stage 2-3 which may in fat be just low GFR rather than actually CKD The above will impact the implications of the study. The authors have to address this

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers' comments
Thank you for your comments. There are our responses. The modified parts of the main file are shown in red font, and the parts that need to be deleted are identified in blue.
Reviewer: 1

1. page 5 "Studies show that compared with traditional prediction models, artificial neural networks have stronger predictive ability and can efficiently identify diseases and high-risk groups in various systems" - but this strong statement is supported only by one existing study. It is an open question whether other machine learning methods would not provide interesting results for the experts, mainly from the point of explainability and interpretability.

(1) After re-analyzing the data, we compared the predictive results of various models constructed by various machine learning algorithms under the same data conditions. These machine learning algorithms included logistic regression, artificial neural network, random forest, decision tree, Bayesian network and support vector machine. The results show that, compared with other machine learning algorithm models, the artificial neural network model has better predictive ability in general, so this paper mainly uses and analyzes the artificial neural network model. See Table 1 for details. (2) In view of the fact that there is only one paper supporting the above statement ("Studies show that compared with...in various systems"), we subsequently added three more papers to support this assertion, and now provide detailed information in the text.

Table 1 Comparison results of multiple machine learning algorithm models

Models	A test set (110 cases)				Accuracy	Specificity	Sensitivity	AUC
	TN	FP	FN	TP				
Logistic regression	69	10	6	25	85.45%	87.34%	80.65%	0.930
Artificial neural network	70	9	6	25	86.36%	88.61%	80.65%	0.913
Random forest	69	10	12	19	80.00%	87.34%	61.29%	0.806
Decision tree	69	10	11	20	80.91%	87.34%	64.52%	0.776
Bayesian network(null=9)	63	11	7	20	82.18%	85.14%	74.07%	0.732
Support vector machine	67	12	7	24	82.73%	84.81%	77.42%	0.927

Abbreviations: TN, true negative; FP, false positive; FN, false negative; TP, true positive; null, missing value

2. page 10 "and the 425 samples were randomly divided into a training set, validation set, persistence set at a ratio of 5:3:2" - it is not clear if the authors used stratified division, i.e., the ratio for the target variable was the same in all three sets.

In this study, the balance node in SPSS Modeler was used to conduct random over-sampling 3.57 times of the cognitive frailty samples in the training set, and the sample size involved a 1:1 ratio of cognitive frailty to non-cognitive frailty cases, which solved the problem of unbalanced target variables. After random over-sampling of the training set, the training set sample, test set sample and verification set sample of the model are 311 cases, 110 cases and 104 cases respectively. The three groups were divided to maintain the consistency of the data distribution as far as possible. The training set (50% of the total sample) included 137 cases of cognitive frailty and 174 cases of non-cognitive frailty. The test set (30% of the total sample) included 31 patients with cognitive frailty and 79 patients with non-cognitive frailty. The verification set (20% of the total sample) included 25 cases of cognitive frailty and 79 cases of non-cognitive frailty.

3. page 3 "... limitations of this study" - it will be important to consider also the unbalanced ratio of the target variable.

Unbalanced data sets refer to the unbalanced sample distribution of target variables in binary data sets, which will easily lead to the insufficient ability of the model to distinguish between minority groups and majority groups and reduce the prediction efficiency of the model. In order to solve this problem, sampling methods, such as over-sampling of minority groups, under-sampling of majority groups or a combination of over-sampling and under-sampling, can be improved.[1] In this study, due to the large difference in the samples of target variables (93 cases of cognitive frailty and 332 cases of non-cognitive frailty). In order to avoid unbalanced problems, the balance node in SPSS Modeler was used to conduct random over-sampling 3.57 times of the cognitive frailty samples in the training set,[2] and the sample size involved a 1:1 ratio of cognitive frailty to non-cognitive frailty cases, after which the ANN model was built. Refs [1] and [2].

[1] Liang F. Application of data mining technology in telecom customer churn. HuaZhong University of Science & Technology. 2019.

[2] Holder LB, Haque MM, Skinner MK. Machine learning for epigenetics and future medical applications. Epigenetics 2017;12:505-514.

Reviewer: 2

1. There are some errors in the grammar in Data collection - Please use Past Tense instead of Present.

We have re-checked the text and corrected the grammatical errors, shown in red font in the main text.

2. The study lacks generalizability as most subjects are primary school graduates and majority have low income. These can be confounding
   There is no control group which can compare the frailty in elderly without CKD.

In this study, due to differences in regional cultural environment and income level, elderly CKD patients with low educational level and income level accounted for a large proportion when randomly sampled, which is consistent with China's national conditions, and also resulted in a higher incidence of cognitive frailty in this study compared with some other studies. This result may be caused by the fact that the randomly selected research subjects of the two hospitals are from the same region, which could affect the generalizability of the findings. Therefore, it is hoped that this shortcoming can be improved through multi-region, multi-center and large-sample studies in future studies.

3. Authors have not mentioned how they diagnosed CKD. It is now very well known that AGING per say can cause lowering of eGFR when calculated and may not represent a TRUE CKD(.https://www.ncbi.nlm.nih.gov/pmc/articles/PM

C4693148/) Authors have also included CKD stage 2-3 which may in fact be just low GFR rather than actually CKD.

In clinical practice, according to the Guidelines for the Screening, Diagnosis and Prevention of Chronic kidney Disease in China (2017), the diagnostic criteria for CKD are as follows: if any of the indicators in the table below occur for more than 3 months, the patient will be diagnosed with CKD. See Table 2 for details.

Table 2 Diagnostic criteria of chronic kidney disease

Sign of kidney injury	(1) Albuminuria[AER≥30mg/24h; ACR≥30mg/g(or≥3mg/mmol)] (2) Abnormal urinary sediment (3) Tubule-related lesions (4) Histological abnormality (5) Imaging findings showed structural abnormalities (6) Kidney transplant history
GFR decline	eGFR<60 mL/min/1.73 m^2

Abbreviations: AER, urinary albumin excretion rate; ACR, urinary albumin creatinine ratio; GFR, glomerular filtration rate

Among them, GFR is the most important indicator for the diagnosis and staging of CKD. At present, MDRD and CKD-EPI formulas are often used to calculate GFR in the elderly in China. According to the current diagnostic criteria for CKD, only a few patients age 60 and older have normal renal function (GFR > 90 mL/min/1.73 m^2), if CKD is diagnosed based on GFR level alone, a significant proportion of the elderly may be overdiagnosed. Therefore, it should be noted that, in clinical practice, a simple mild decline in GFR (GFR 60~89 mL/min/1.73m^2) without any other manifestations of kidney injury should not be considered as having CKD. When the GFR<60 mL/min/1.73m^2 (over 3 months), patients could be treated as CKD stage 3. However, there are still highly controversial that a fixed GFR threshold of <60 mL/min/1.73m^2 to define CKD leads to overdiagnosis in the elderly. According to the Chinese expert consensus on the diagnosis and treatment of chronic kidney disease in the elderly (2018), in view of the Scr-based GFR formulas (such as MDRD and CKD-EPI formulas) for assessing renal function that may overestimate the prevalence of CKD stage 3a (GFR 45-59 mL/min/1.73m^2), in order to reduce overdiagnosis of CKD stage 3a, the guidelines of Kidney Disease: Improving Global Outcomes (KDIGO) in 2012 recommended that further estimates of GFR based on cystatin C (such as the CKD-EPIcr-cyst formula) for CKD in patients with GFR 45~59 mL/min/1.73m^2 and no evidence of kidney injury. In this study, 22 elderly patients with CKD stage 3 were included, including 4 patients with CKD stage 3a and 18 patients with stage 3b. The relevant information is shown in Table 3.

Table 3 eGFR calculation results in elderly patients with CKD stage 3a

							eGFR[mL/min/1.73 m^2]	
Cases	The sample number	Age	Gender	Scr (μmol/L)	Cys-C (mg/L)	AER (g/24h)	CKD-EPI	CKD-EPIcr-
1	146	65	male	139.20	1.33	0.313	45.415	55.655
2	153	61	male	136.90	1.61	5.656	47.659	50.265
3	319	65	male	123.30	2.86	1.160	52.588	36.977
4	341	68	female	104.10	1.49	0.903	47.621	42.571

Abbreviations: Scr, serum creatinine; Cys-C, cystatin C; AER, urinary albumin excretion rate

As shown in Table 3, no overdiagnosis was observed by re-examining the elderly patients in stage 3a with the CKD-EPIcr-cyst formula, and 4 patients were accompanied by albuminuria (AER≥0.03g/24h), which met the diagnostic criteria. The table showed that there were two patients in stage 3a and two in stage 3b, both of which were elderly patients with CKD stage 3. If GFR < 60 mL/min/1.73 m^2 is used as the staging threshold for CKD stage 2 and CKD stage 3 at any age according to the previous diagnostic criteria for CKD, a considerable degree of overdiagnosis may be caused in the elderly. Therefore, the KDIGO guideline added two staging indicators on the basis of K/DOQI guideline, included cause and albuminuria, and proposed the "three-dimensional staging" method of Cause-GFR-Albuminuria (CGA). In this study, 5 elderly patients with CKD stage 2 were included, the relevant information is shown in Table 4.

Table 4 the relevant information in elderly patients with CKD stage 2

						eGFR[mL/min/1.73 m^2]
Cases	The sample number	Age	Gender	Scr (μmol/L)	AER (g/24h)	CKD-EPI
1	133	66	male	91.70	0.924	74.697
2	275	64	male	92.87	2.016	74.602

3	296	67	male	84.40	3.654	81.999
4	301	75	male	96.24	1.075	66.142
5	418	72	male	85.76	4.117	77.654

Abbreviations: Scr, serum creatinine; AER, urinary albumin excretion rate

As shown in Table 4, no overdiagnosis was observed by re-examining the elderly patients in CKD stage 2 with the CKD-EPI formula, and 5 patients were accompanied by albuminuria (AER≥0.03g/24h), which met the diagnostic criteria.

The 425 samples collected in this study were all elderly patients with definite diagnosis of CKD stage 2-5 in the medical records.

Abstract

Objective To investigate the risk factors of cognitive frailty in elderly patients with chronic kidney disease (CKD), and to establish an artificial neural network (ANN) model.

Design A cross-sectional design.

Setting Two tertiary hospitals in southern China.

Participants 425 elderly patients of age ≥60 years with CKD.

Methods Data were collected via questionnaire investigation, anthropometric measurements, laboratory tests and electronic medical records. The 425 samples were randomly divided into a training set, test set and validation set at a ratio of 5:3:2. Variables were screened by univariate and multivariate logistic regression analysis, then an ANN model was constructed. The accuracy, specificity, sensitivity, receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to evaluate the predictive power of the model.

Results BI score, albumin, education level, GDS-15 score and SSRS score were the factors influencing the occurrence of cognitive frailty ($P<0.05$). Among them, BI score was the most important factor determining cognitive frailty, with an importance index of 0.30. The accuracy, specificity and sensitivity of the ANN model were 86.36%, 88.61% and 80.65%, respectively, and the AUC of the constructed ANN model was 0.913.

Conclusion The ANN model constructed in this study has good predictive ability, and can provide a reference tool for clinical nursing staff in the early prediction of cognitive frailty in a high-risk population.

Strengths and limitations of this study

- Cognitive frailty is highly prevalent among elderly patients with CKD, and early prediction and intervention can prevent the occurrence or development of cognitive frailty.
- Artificial neural networks (ANN) have stronger predictive ability compared with traditional prediction models, the ANN model can provide a new reference tool for clinical practice.

- The larger the sample size, the better the prediction power of the model. In the future, it is still necessary to increase the sample size to improve the prediction power of the model.
- This study was conducted in only one city of China, which could affect the generalizability of the findings.

INTRODUCTION

The number of people 60 years of age and over is expected to double by 2050, according to a new report released by the World Health Organization (WHO), with aging and super-aging becoming increasingly serious worldwide.[1] As the most populous country in the world, China has a particularly prominent aging problem.[2] According to the Social Bulletin of the National Bureau of Statistics in 2019, by the end of 2019,the population over the age of 60 in China had reached 254 million,[3] and it is expected that by 2050, the total elderly population over the age of 60 in China will reach 498 million.[4] Chronic kidney disease (CKD) is a chronic decomposing metabolic disease that has become a major global public health problem among the elderly, with a prevalence of 32%-37% in the elderly population,[5] and increases with age.[6] Aging is associated with physical frailty and cognitive decline.[7] The incidence of cognitive decline in the elderly in China is 22%, increases with age, and is especially high in patients with chronic diseases such as CKD.[8] Cognitive decline can affect the social function and quality of life of the elderly to varying degrees, and even death.[9]

Physical frailty is a geriatric syndrome characterized by a cumulative decline in multi-system physiological functions.[7] The incidence of physical frailty in elderly patients with CKD can be as high as 73%, and is closely related to adverse health outcomes such as prolonged hospital stay, increased risk of falls, cardiovascular events and even death.[10] Several studies have shown a tight and interactive relationship between frailty and cognitive decline due to many common risk factors and mechanisms.[11, 12] Elderly patients are considered to have cognitive frailty when having both physical frailty and cognitive decline, excluding dementia, which increases the risk of adverse health outcomes.[13] It has been reported that the incidence of cognitive frailty in communities and hospitals is 1.0%~39.7%.[14, 15] Elderly patients with CKD are often at greater risk of cognitive frailty due to anemia, inflammatory vascular diseases and various metabolic disorders.[16] Several studies have found that the prevalence of cognitive frailty in elderly hemodialysis patients ranges from 4.6% to 25.9%.[17, 18] However, there are still few studies and limited evidence on cognitive frailty in elderly patients with CKD, and the reported prevalence varies greatly due to differences in the population studied and the measurement tools used. In addition, the influencing factors of cognitive frailty include physiological, psychological, social and geriatric syndromes. Previous literature has shown that gender, age, education level, income level, physical exercise, disease type, nutrition, sleep and psychological status, creatinine, hemoglobin, albumin and other factors are related to the occurrence of cognitive frailty.[18-21] Moreover, the reversible characteristics of cognitive frailty make it possible to be prevented, delayed or reversed through early prediction and intervention. (delete)cognitive frailty is potentially reversible, and the occurrence or development can be prevented by prediction and intervention as early as possible. Therefore, it would be of great significance to construct a prediction model of cognitive frailty for accurate prediction and intervention in high-risk population.

However, at present, prediction models have been mainly based on traditional regression analysis, and less on other machine learning algorithms. An artificial neural network (ANN) is a multi-layer complex model with multiple neurons as nodes and synaptic connections.[22] Studies show that, in various systems, compared with traditional rules-based or regression-based models, artificial neural networks have stronger predictive ability and can efficiently identify diseases and high-risk groups.[23-26] Moreover, ANN models have obvious advantages in data processing, identification and data fitting.[27] Therefore, this study constructed an ANN model for early risk prediction of cognitive frailty in elderly patients with CKD, aiming to provide a new reference tool for the early prediction of cognitive frailty in elderly patients with CKD, as well as assist clinical medical workers to quickly identify the risk of cognitive frailty in elderly patients with CKD, and provide a basis for the formulation and implementation of early intervention. (delete)aiming to provide an effective tool for nurses to identify high-risk populations early, thus providing scientific guidance for follow-up clinical nursing work.

METHODS

Study design and setting

This cross-sectional study was conducted from October 2020 to August 2021 in two tertiary hospitals in Shantou, Guangdong Province, China. Convenience sampling was used to collect data in the Department of Nephrology.

Data collection and ethical considerations

After we contacted and obtained the consent of the two department directors, we invited the department nurses to assist in collecting data. We introduced the purpose of this study to patients in a unified guidance language. After obtaining written informed consent from the patient, a one-to-one survey was conducted by 2 uniformly trained investigators, and grip strength and body weight was measured by using uniform methods and equipment. The data in this study was obtained from questionnaire investigation, anthropometric measurements, laboratory tests and electronic medical records. This study was approved by the university institutional review board (SUMC-2020-77).

Participants

A total of 430 elderly patients with chronic kidney disease were recruited from southern China. For selection criteria, subjects were required to have been (1) diagnosed with chronic kidney disease, (2) at least 60 years of age, (3) without dementia, visual or hearing impairment, and (4) a voluntary participant in the study. Of the 430 participants, 5 were excluded for complicated malignancies, chronic malnutrition, or having acute kidney injury within 3 months. Ultimately, a total of 425 patients were included, with a response rate of 98.84%.

Sample size was calculated according to the sample size estimation method used in epidemiological cross-sectional studies, , where n is the sample size, Z represents statistic, 1-α/2 represents a two-sided test, P is the disease prevalence, and d represents precision. Previous studies found that the prevalence of cognitive frailty in elderly patients with CKD was 25.9%.[18] We assumed a confidence level of 95% with a precision of 5% and adopted a two-sided test, taking into account a 20% non-response rate. Therefore, the minimum sample size required for this study was 295 cases.

Survey instrument

Frailty

Frailty status was assessed by the Frailty Phenotype (FP) defined by Fried et al.[28] The scale includes 5 components: unintentional weight loss, grip strength decline, self-rated exhaustion, low gait speed and physical activity. The total score ranges from 0 to 5, and patients with 3 or more components were classified as frail, whereas those with fewer than 3 components were classified as non-frail.

Functional status

The Barthel Index (BI) was used to assess the capacity for daily living.[29] The scale consists of 10 items, for a total score of 100 points, and is graded as severe dependency (score≤40), moderate dependency (41≤score≤60), mild dependency (61≤score≤99) and complete independence. The Cronbach's alpha coefficient of the BI was 0.88, indicating good reliability and validity.[30]

Nutritional status

In the survey, the Mini-Nutritional Assessment-Short Form (MNA-SF) was used to assess nutritional status, and was simplified from the MNA by selecting 6 items to evaluate the risk of malnutrition over the past three months.[31] The total score of the MNA-SF ranges from 0 to 14, with a score of less than 11 indicating malnutrition. According to previous research, the scale has good specificity and sensitivity.[32]

Sleep quality

Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI) in the survey, which was created from Buysse et al.[33] The scale is a validated measurement tool to screen for sleep disturbances, and includes 19 self-rated items and 5 other-rated items of which 7 components are composed of 18 self-rated items. The 7 components are as follows: subjective sleep quality, falling asleep time, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Each component is scored from 0 to 3 points, and the total score ranges from 0 to 21 points by summing the 7 component scores. A total score greater than 7 points indicates poor sleep quality. It has been widely usd in the Chinese population, and the Cronbach's alpha coefficient for the PSQI was 0.842.[34]

Cognitive status

The Mini-Mental State Examination (MMSE) was used to screen cognitive status in the survey. The MMSE is comprised of 7 dimensions with 30 items, and the total score ranges from 0 to 30, with a higher score indicating higher level of cognitive function.[35] The scale was divided according to the educational level of participants: ≤17 points—illiterate; ≤20 points—primary school; ≤24 points—secondary school and above. The Cronbach's alpha coefficient of the MMSE was 0.898.[36]

Depressive symptoms

The 15-item GDS (GDS-15) was used to assess depression within the past week, and was simplified from Sheikh et al.[37] The total score of the GDS-15 ranges from 0 to 15, with a score of 8 or more indicating the presence of depressive symptoms. The Cronbach's alpha coefficient of GDS-15 was 0.793 in the elderly population of China.[38]

Social function

The Social Support Rating Scale (SSRS) was used to evaluate the level of family social support.[39] The SSRS is comprised of 3 dimensions with 10 items, including objective support, subjective support and utilization of social support, which ranges from 12 to 66 points. The higher the score, the better the family social support, among them, ≤22 is classified as low-level, 23-44 as medium-level and ≥45 as high-level support. The Cronbach's alpha coefficient of the SSRS was 0.825~0.896.

Covariates

The covariates included sociodemographic data, physical indicators, living habits, physical health status and laboratory indices. Sociodemographic data included age, gender, education level, occupation before retirement, monthly income, hospitalization payment method, and mobility aids (yes or no) such as walking stick or wheelchair. Living habits were included, such as smoking, drinking, falling down in the past year (yes or no) and the number of times of exercise per week. Physical health status (CKD stage, dialysis status, comorbidity, polypharmacy) and laboratory indices (C-reactive protein, parathormone, ferritin, albumin, blood urea nitrogen, creatinine, total cholesterol, triglycerides, white blood cells, hemoglobin, glomerular filtration rate) were obtained from the electronic medical records. Physical indicators (height, body weight, BMI, blood pressure, grip strength) were measured by 2 trained interviewers by using the electronic grip dynamometer (Xiangshan EH101), the electronic sphygmomanometer arm, the scale and the flexible rule.

Statistical analysis

Data was double-entered using Epidata3.1, and SPSS version 25.0 and SPSS Modeler 18.0 software were used for statistical analysis and construction of the predictive model. Count data was presented as frequencies and percentages, and the comparison between groups was performed by the χ^2 test. When metrological data conformed to a normal distribution, results were expressed as mean ± standard deviation, and the t-test was used for comparison of the groups. Otherwise, median and interquartile range were used for statistical description, and the comparisons were analyzed by the Mann-Whitney U test. Variable screening was conducted by using univariate analysis with an α significance level of 0.05. The variables that conformed to colinear diagnosis and statistically significant ($P<0.05$) were included in the binary logistic regression analysis for inclusion in the final model. Through the binary logistic regression analysis in the study, the results showed that there were 5 variables with statistical significance ($P<0.05$), and were ultimately included in the prediction model. Cognitive frailty was considered as a dichotomous dependent variable in the study, and the 425 samples were randomly divided into a training set, test set and validation set at a ratio of 5:3:2 by using a multilayer perceptron artificial neural network. The random number seed was 1234567. The training set was used for building the model, the validation set was used to optimize the model parameters, whereas the test set was used for evaluation. Due to the large difference in the samples of target variables (93 cases of cognitive frailty and 332 cases of non-cognitive frailty), in order to avoid the problem that unbalanced data sets lead to the degradation of model prediction power, the balance node in SPSS Modeler was used to conduct random over-sampling 3.57 times of cognitive frailty samples in the training set, [40] and the sample size involved a 1:1 ratio of cognitive frailty to non-cognitive frailty cases, after which the ANN model was built. The accuracy, sensitivity, specificity, receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to evaluate the predictive power of the ANN model.

Patient and public involvement

The patients were not involved in the formulation of the study questions or the design of the study. The results of the study are not intended to be released to the participants, but anthropometric measurements taken during the survey were provided to the participants.

RESULTS

Study sample characteristics

Of the 430 participants enrolled in the study, 5 were excluded from the study for comorbidity with other severe diseases, and the questionnaire had a 98.8% response rate. The majority of the participants were male (60.2%) and the mean age was 68.5 years. There was a predominance of individuals who were primary school graduates and below (58.8%), and had other occupations (66.4%) before retirement, low monthly income (43.5%), little to no movement (77.2%) and normal BMI (18.5≤BMI<24.9, 64.2%), and moved without mobility aids (88.7%). The prevalence was 21.9% (n=93) for cognitive frailty and 78.1% (n=332) for non-cognitive frailty. Participants with cognitive frailty were more likely to be older, have lower levels of education, move without mobility aids, lack exercise, have comorbidity with other chronic diseases, and take three or more medications. The capacity for daily living, nutritional status, sleep quality and social activity were also poor, and depressive symptoms and abnormal laboratory indices were also common (Table 1).

Table 1

Characteristics of the study population

Variables	Total （n=425）	Cognitive frailty （n=93）	Non-cognitive frailty（n=332）	Statistics values	P
Age, years, M (P_{25}, P_{75})	67 (63, 73)	69 (64, 76.50)	67 (63, 72)	-2.387 2)	0.017
BMI, Mean±SD	22.91±3.53	22.10±3.56	23.14±3.49	2.511 1)	0.012
Gender, n (%)				3.661 3)	0.056
male	256 (60.2)	64 (68.8)	192 (57.8)		
female	169(39.8)	29 (31.2)	140 (42.2)		
Education level, n (%)				32.173 3)	<0.001
Primary school and below	250 (58.8)	31 (33.3)	219 (66.0)		
Junior high /high school	144 (33.9)	50 (53.8)	94 (28.3)		
College and above	31 (7.3)	12 (12.9)	19 (5.7)		
Occupation before retirement, n (%)				4.652 3)	0.199
farmer	77 (18.1)	12 (12.9)	65 (19.6)		
worker	53 (12.5)	8 (8.6)	45 (13.6)		
intellectual	13 (3.1)	3 (3.2)	10 (3.0)		
others	282 (66.4)	70 (75.3)	212 (63.9)		
Monthly income (yuan), n (%)				4.157 3)	0.125
≤3000	185 (43.5)	32 (34.4)	153 (46.1)		
3000~5000	169 (39.8)	44 (47.3)	125 (37.7)		
≥5000	71 (16.7)	17 (18.3)	54 (16.3)		
Mobility aids, n (%)				15.137 3)	<0.001

No	377 (88.7)	72 (77.4)	305 (91.9)		
Yes	48 (11.3)	21 (22.6)	27 (8.1)		
Exercise [times/week], n (%)				17.013 3)	<0.001
0	328 (77.2)	86 (92.5)	242 (72.9)		
1~2	39 (9.2)	5 (5.4)	34 (10.2)		
≥3	58 (13.6)	2 (2.2)	56 (16.9)		
CKD stage, n (%)				0.191 3)	0.662
CKD stage 2-3	27 (6.4)	5 (5.4)	22 (6.6)		
CKD stage 4-5	398 (93.6)	88 (94.6)	310 (93.4)		
Dialysis, n (%)				0.348 3)	0.555
No	208 (48.9)	43 (46.2)	165 (49.7)		
Yes	217 (51.1)	50 (53.8)	167 (50.3)		
Heart failure, n (%)				5.010 3)	0.025
No	296 (69.6)	56 (60.2)	240 (72.3)		
Yes	129 (30.4)	37 (39.8)	92 (27.7)		
Hyperuricemia, n (%)				4.947 3)	0.026
No	393 (92.5)	91 (97.8)	302 (91.0)		
Yes	92 (7.5)	2 (2.2)	30 (9.0)		
SHPT, n (%)				5.812 3)	0.016
No	359 (84.5)	86 (92.5)	273 (82.2)		
Yes	66 (15.5)	7 (7.5)	59 (17.8)		
BI score, M (P_{25}, P_{75})	90 (70, 95)	65 (50, 80)	95 (80, 95)	-8.940 2)	<0.001
MNF-SF score, M (P_{25}, P_{75})	11 (9, 12)	9 (7, 11)	11 (9, 13)	-6.071 2)	<0.001
PSQI score, M (P_{25}, P_{75})	8 (5, 12)	10 (6.5, 14.5)	7 (5, 12)	-3.284 2)	0.001
GDS-15 score, M (P_{25}, P_{75})	6 (3, 9)	9 (6, 11)	4 (2.25, 8)	-7.457 2)	<0.001
SSRS score, M (P_{25}, P_{75})	38 (34, 43)	36 (32, 38)	39.5 (35, 44)	-5.807 2)	<0.001
CRP, M (P_{25}, P_{75})	10.9 (3.15, 29.33)	25.3 (6.14, 60.2)	8.46 (2.79, 29.33)	-4.474 2)	<0.001
Parathormone, M (P_{25}, P_{75})	252.1 (109.95, 412.35)	265.80 (118.75, 358.80)	248.40 (109.53, 425.08)	-0.449 2)	0.653
Ferritin, M (P_{25}, P_{75})	288.6 (125.25, 408.3)	350.21 (184.55, 500.1)	266.95 (118.7, 397.38)	-2.264 2)	0.024
Albumin, Mean±SD	31.12±5.4	29.80±4.99	31.48±5.47	2.667 1)	0.008
BUN, M (P_{25}, P_{75})	21.47 (15.43, 29.63)	21.26 (15.22, 29.31)	21.68 (15.50, 29.64)	-0.341 2)	0.733
Scr, M (P_{25}, P_{75})	641.21 (411.05, 868.28)	616.87 (464.75, 820.42)	645.64 (400.23, 880.75)	-0.406 2)	0.685
TC, M (P_{25}, P_{75})	4.31 (3.29, 5.31)	3.7 (3.02, 4.92)	4.42 (3.45, 5.41)	-3.141 2)	0.002
Triglycerides, M (P_{25}, P_{75})	1.29 (0.88, 1.82)	1.17 (0.79, 1.80)	1.30 (0.92, 1.82)	-1.579 2)	0.114
WBC, M (P_{25}, P_{75})	7.03 (5.67, 8.75)	7.57 (6.11, 9.07)	6.92 (5.61, 8.59)	-2.059 2)	0.040
Hemoglobin, M (P_{25}, P_{75})	90 (75, 105.5)	87 (72, 102.5)	91 (76, 106)	-1.294 2)	0.196

GFR, M (P_{25}, P_{75})	6.96 (5.1, 11.51)	7.48(5.79, 10.41)	6.73 (4.97, 12.08)	-1.050 2)	0.294

Note: 1) T-value；2）Z-value；3）χ^2-value

Abbreviations: BMI, body mass index; SHPT, secondary hyperparathyroidism; CRP, C-reactive protein; BUN, blood urea nitrogen; Scr, serum creatinine; TC, total cholesterol; WBC, white blood cell; GFR, glomerular filtration rate

Logistic regression analysis of cognitive frailty in elderly patients with chronic kidney disease

The variables that conformed to colinear diagnosis and statistically significant (P<0.05) in univariable analysis were included as independent variables, cognitive frailty was included as the dependent variable in the binary logistic regression analysis, and variable assignments are shown in Table 2. The results of the binary logistic regression analysis showed that education level, BI score, albumin, GDS-15 score and SSRS score were the factors for cognitive frailty (P<0.05) (Table 3).

Table 2

Assignment of independent variables

Variables	Assignment method
Cognitive frailty	Non-cognitive frailty=0; cognitive frailty=1
Age	Original value entry
BMI	Original value entry
Gender	Female=0; male=1
Education level	Primary school and below=0; junior high /high school=1; college and above=2
Occupation before retirement	Farmer=0; worker=1; intellectual=2; others=3
Monthly income (yuan)	≤3000=0; 3000~5000=1; ≥5000=2
Mobility aids	No=0; Yes=1
Exercise [times/week]	0=0; 1~2=1; ≥3=2
CKD stage	CKD stage 1-3=0; CKD stage 4-5=1
Dialysis	No=0; Yes=1
Heart failure	No=0; Yes=1
Hyperuricemia	No=0; Yes=1
SHPT	No=0; Yes=1
BI score	Original value entry
MNF-SF score	Original value entry
PSQI score	Original value entry
GDS-15 score	Original value entry
SSRS score	Original value entry
CRP	Original value entry
Parathormone	Original value entry
Ferritin	Original value entry
Albumin	Original value entry
BUN	Original value entry
Creatinine	Original value entry
TC	Original value entry
Triglycerides	Original value entry
WBC	Original value entry
Hemoglobin	Original value entry
GFR	Original value entry

Table 3

Logistic regression analysis for cognitive frailty

Variables	β	S.E	Wald χ^2	P	OR	95%CI
Constant	15.383	5.178	8.826	0.003	-	-
Education level	2.566	0.401	40.896	<0.001	13.009	5.926~28.560
BI score	-0.035	0.010	12.908	<0.001	0.965	0.947~0.984
Albumin	-0.070	0.033	4.462	0.035	0.932	0.873~0.995
GDS-15 score	0.183	0.061	9.053	0.003	1.201	1.066~1.354
SSRS score	-0.111	0.033	11.053	0.001	0.895	0.838~0.955

Construction and validation of the cognitive frailty risk prediction model

The neural network prediction model in this study included one input layer, one hidden layer and one output layer. Variables with statistical significance (P<0.05) in the binary logistic regression analysis were considered as the input layer, included 5 variables. Whether cognitive frailty was regarded as the output layer, the hidden layer had 6 neurons, and a hyperbolic tangent function was used for activation. In order to avoid the problem of unbalanced target variables, the samples were randomly divided into training set (311 cases), test set (110 cases) and validation set (104 cases) after random over-sampling 3.57 times of cognitive frailty samples in the training set. Then, the prediction model of the multi-layer perceptron neural network was constructed (See supplementary file 1). The accuracy, specificity and sensitivity of the ANN model were 86.36%, 88.61% and 80.65%, respectively. (delete)The ANN model had training set, validation set, persistence set accuracies of 87.8%, 88.0% and 83.5%, respectively. The area under ROC curve (AUC) was 0.913, the receiver operating characteristic curve (ROC) as shown in supplementary file 2. In order, the normalized importance of the independent variables of the ANN model was as follows: BI score, SSRS score, albumin, GDS-15 score and education level (See supplementary file 3).

DISCUSSION

Cognitive frailty is a reversible or potentially reversible heterogeneous clinical syndrome that can significantly increase the risk of a series of adverse health outcomes, such as falls, hospitalization, cardiovascular events and even death in the elderly. In particular, older adults with chronic diseases such as CKD are at greater risk.[16] It is undeniable that early cognitive frailty screening and effective intervention can greatly aid in reversing cognitive frailty. However, the reported prevalence of cognitive frailty varies widely due to differences in study populations and assessment methods. In this study, we found that 21.9% of older patients with CKD have cognitive frailty, which is comparable to a previous study involving cognitive frailty of hemodialysis patients in China,[18][31] but quite different from a study on the prevalence of cognitive frailty in hemodialysis patients in the USA.[17] In addition, our findings suggest that the main influencing factors for cognitive frailty are BI score, albumin, education level, GDS-15 score and SSRS score.

We found that the capacity for daily living is an independent risk factor for cognitive frailty, indicating that a substantial perentage of elderly patients with CKD are not fully independent for daily living, which is in line with a previous study in the USA.[41] Research has shown that when the capacity for daily living is impaired, the perception of the external environment also can be correspondingly abated, thus reducing brain activity, at the same time, leading to muscle atrophy and strength decline, thereby increasing the patient's physical fatigue, and further leading to increased risk of cognitive frailty.[42] However, impairment of the capacity for daily living is common in elderly patients with CKD, which also highlights the importance of the capacity for daily living assessment.

The Barthel Index (BI) was used to assess the capacity for daily living in our study, which is common in the clinic. It enables nursing staff to identify problems with the living ability of patients early, in order to determine a nursing and intervention plan as soon as possible to improve the patient’s quality of life.[43]

In this study, we show that serum albumin is one of the important indexes for evaluating cognitive frailty in patients, and a normal range of serum albumin may reduce the risk of cognitive frailty, which is consistent with other studies.[18, 44, 45] However, due to the decline of renal function, long-term restriction of protein intake, inflammation, long-term dialysis and other reasons, elderly patients with CKD are prone to protein loss and malnutrition, resulting in sarcopenia, which is also related to cognitive frailty.[16] All in all, medical staff should regularly monitor patient serum albumin, hemoglobin and other nutritional indicators, and take positive treatment measures for patients with malnutrition and chronic inflammation, so as to maintain the nutritional status of patients and prevent the occurrence of cognitive frailty. In addition, encouraging patients to adhere to a Mediterranean diet may reduce the risk of cognitive decline to some extent.[46]

We further found that the rate of cognitive frailty is lower among those with high education levels, in agreement with studies by others.[47, 48] On the one hand, the reason may be related to the fact that early education training received by patients with a high education level can effectively increase brain reserve and delay brain degeneration.[48] On the other hand, older patients with higher education have a better grasp of disease-related knowledge, which can further improve patient treatment compliance and prevent the occurrence and progression of cognitive frailty.[49] However, most patients included in this study had a primary school education or below, which may be the reason for the higher incidence of cognitive frailty than seen in some other studies. Therefore, nursing staff should pay attention to elderly people with different educational levels and CKD, formulate corresponding health education content and intervention measures according to the specific needs of each patient, and guide patients to be familiar with and master knowledge of the disease, so as to prevent or delay the occurrence and progression of cognitive frailty.

The results of our study also suggest that depression and low social support are risk factors for cognitive frailty, which is consistent with Malek et al.[20] Elderly patients with CKD are prone to anxiety, depression and other adverse emotions due to the long course of the disease and long-term frequent dialysis and hospitalization, as well as the weakening of social participation and functions.[49] In addition, there is a similar pathological basis between depression and cognitive frailty, which makes the two closely related.[50] Paying attention to a patient's emotional changes, communicating with the patient more, encouraging the patient to participate in social activities, and encouraging family members and friends to listen to and accompany the patient can relieve bad mood to a certain extent. Social support is not only closely related to physical and mental health, but also affects individual emotion, thought and behavior, which plays a key role in the trajectory of cognitive frailty. High levels of social support is a protection factor in cognitive frailty, because patients not only receive emotional and financial support, but also obtain access to more health information resources, such as diet or exercise guidance, through the transfer and use of social resources, all of which can effectively improve the patient's physical and mental health.[51]

(delete)In this study, we show that the use of mobility aids and reduction in exercise time may affect cognitive frailty. In elderly patients with CKD, the comorbidity group accounts for a large proportion, which will aggravate organism aging, promote the loss of calcium, the decrease physiology and dysregulate balance in the body,[35] and these factors will bring about a reduction of physical activity or increase the dependence on mobility aids in elderly patients. At the same time, older patients are considered to be socially isolated due to limited activity and a narrower social circle, which further reduces physical activity.[36]

(delete)The results of our study also suggest that abnormal lipid metabolism and secondary hyperparathyroidism, caused by a metabolic disorder of calcium and phosphorus, may contribute to cognitive frailty. Abnormal lipid metabolism, such as higher levels of total cholesterol, could affect the vessels of the brain and the metabolism in neuronal cells, and accelerate vascular stiffening, finally resulting in cognitive frailty.[39] At the same time, secondary hyperparathyroidism is ubiquitous in patients with CKD. However, excessive parathormone synthesis could worsen the hardening of blood vessels and further affect brain function, leading to cognitive frailty, similar to a previous study that showed the higher the levels of parathormone, the more severe the degree of frailty.[40]

Through various training algorithms, artificial neural networks can analyze the input variables that affect the dependent variables, and construct a predictive model with higher accuracy than the traditional logistic regression model.[22] In our study, we incorporated physiological, psychological, social and geriatric syndromes, and other aspects into an artificial neural network to predict cognitive frailty in elderly patients with CKD. Five variables were ultimately included through univariate and multivariate analysis to construct an ANN model. The accuracy, specificity and sensitivity of the ANN model were 86.36%, 88.61% and 80.65%, respectively, and the AUC of the constructed ANN model was 0.913, indicating that the model has good predictive power for the occurrence of cognitive frailty in elderly patients with CKD. In addition, the results of our study also suggest that the BI score is the most important factor determining cognitive frailty in the analysis of independent variables, with an importance index of 0.30. Therefore, elevating patient capacity for daily living can protect against cognitive frailty in elderly patients. In clinical practice, the probability of cognitive frailty of elderly patients with CKD can be obtained by a neural network algorithm, based on the actual situation of the patients and the corresponding independent variables, with high accuracy and practicability in the clinic.

Two limitations should be mentioned in our study. In terms of the machine learning model, the larger the sample size, the better the prediction power of the model. In the future, it will still be necessary to increase the sample size to improve the prediction power of the model. In addition, the study was conducted in only one city in China, which could affect the generalizability of the findings.

CONCLUSIONS

This cross-sectional study of showed a 21.9% prevalence of cognitive frailty among older Chinese patients with CKD. BI score, albumin, education level, GDS-15 score and SSRS score are the main influencing factors for cognitive frailty. An ANN model, based on these factors, has good predictive accuracy, can provide a new reference tool for the early prediction of cognitive frailty in elderly patients with CKD, and enable a basis for the implementation of early intervention.

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ORCID iDs

Baolin Luo https://orcid.org/0000-0001-7486-6278

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VERSION 2 – REVIEW

REVIEWER	Babic, Frantisek Technical University of Košice Faculty of Electrical Engineering and Informatics

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GENERAL COMMENTS	Thank you for incorporating my recommendations and comments.